

# **EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF CHLOROFORM**

Reproductive and Cancer Hazard Assessment Section (RCHAS)  
Office of Environmental Health Hazard Assessment (OEHHA)  
California Environmental Protection Agency (Cal/EPA)



# CHLOROFORM (CAS No. 67-66-3)

- Trichloromethane:  $\text{CHCl}_3$
- Annual U.S. production over 500 million pounds
- By-product of water disinfection by chlorine
- Exposure may occur in the workplace, via consumption of contaminated water, or via exposure to vapor of contaminated water



## PHARMACOKINETICS OF CHLOROFORM

- Absorbed by oral, inhalation, or dermal routes
- Rapid distribution throughout the body
  - Crosses placenta
  - Expected to appear in breast milk
- Metabolized by cytochrome P450-dependent pathways
- Non-metabolized chloroform excreted via exhalation



# **Non-DART Effects of Chloroform**

## **Acute Effects:**

- Anesthesia
- Liver necrosis
- Death

## **Chronic Effects:**

- Neurological effects
- Cytotoxicity in liver, kidney, and nasal mucosa

## **Carcinogenicity:**

- Proposition 65 carcinogen



## **Developmental Toxicity of Chloroform by Inhalation in the Rat (1a)**

*Schwetz et al., 1974 – 0, 30, 100, 300 ppm*

- Decreased pregnancy rate, litter size, fetal weight and length, altered sex ratio (300 ppm)
- Increased gross anomalies (100 ppm)
- Increased skeletal anomalies, decreased length (30 ppm)
- Reduced maternal body weight (300 ppm)



## Developmental Toxicity of Chloroform by Inhalation in the Rat (1b)

*Schwetz et al., 1974* – feed restricted control group

	Feed restricted	300 ppm
Feed gd 12-13 (% ad lib control)	17%	4%
Pregnant/bred	8/8	3/20
Maternal wt gd 13 (% ad lib control)	72%	62%
Fetal weight at term (% ad lib control)	91%	60%



## Developmental Toxicity of Chloroform by Inhalation in the Rat (2)

*Baeder & Hoffman, 1988 – 0, 30, 100, 300 ppm*

- Decreased fetal length (30, 100, 300 ppm)
- Decreased litters, and fetal weight (300 ppm)
- Reduced maternal body weight (30, 100, 300 ppm)

*Baeder & Hoffman, 1991 – 0, 3, 10, 30 ppm*

- Decreased fetal weight and length (30 ppm)
- Increased ossification variations (3, 10, 30 ppm)
- Reduced maternal body weights (10, 30 ppm)



## **Developmental Toxicity of Oral Chloroform in the Rat; by Gavage**

*Thompson et al., 1974 – 0, 20, 50, 126 mg/kg-day*

- Decreased fetal weights (126 mg/kg-day)
- Decreased maternal weight gain (50, 126 mg/kg-day)

*Ruddick et al., 1983 – 0, 100, 200, 400 mg/kg-day*

- Decreased fetal weight (400 mg/kg-day)
- Decreased maternal weight gain (100, 200, 400 mg/kg-day)





## **Developmental Toxicity of Chloroform by Inhalation in the Mouse**

*Murray et al., 1979* – 0, 100 ppm on gestation days 1-7, 6-15, or 8-15

- Decreased pregnancy rate (days 1-7 or 6-15)
- Increased resorptions (days 1-7)
- Decreased fetal body weight and length (days 1-7 or 8-15)
- Increased cleft palate & retarded ossification of sternebrae (days 1-7 or 8-15)
- Decreased maternal weight gain (days 1-7 or 8-15)



## **Developmental Toxicity of Oral Chloroform in the Rabbit; by Gavage**

*Thompson et al., 1974 – 0, 20, 35, 50 mg/kg-day*

- Decreased fetal weights (20, 50 mg/kg-day)
- Excess maternal death (50 mg/kg-day)
- Decreased maternal weight gain (50 mg/kg-day)



## **Developmental Neurotoxicity of Oral Chloroform in the Mouse; by Gavage**

*Burkhalter and Balster, 1979* – 31.1 mg/kg-day, prior to mating, throughout gestation, lactation, and to pups

- Reduced postnatal weight gain (31.1 mg/kg-day)
- Lower scores for forelimb placement, postnatal days 5 and 7 (31.1 mg/kg-day)
- Maternal effects not discussed



# Male Reproductive Toxicity of Chloroform in Mice

## Inhalation Sperm Study

*Land et al., 1979 & 1981* – 0, 400, 800 ppm (roughly 0, 450, 900 mg/kg-day)

- Abnormal sperm morphology

## Gavage Continuous Breeding Study

*NTP, 1988* – 0, 6.6, 15.9, 41.2 mg/kg-day

- No effects on fertility or sperm parameters
- Increased epididymal weight in F1 generation



# Female Reproductive Toxicity of Chloroform (1)

*NTP, 1988* – 0, 6.6, 15.9, 41.2 mg/kg-day

- Continuous breeding study in mice, by gavage
- No adverse reproductive effects

*U.S. EPA, 1980* – 0, 20, 38, 57, 81, 160 mg/kg-day

- 90-day toxicity study in rats, drinking water
- No effects on ovaries or uterus

*Heywood et al., 1979* – 0, 15, 30 mg/kg-day

- 7.5-year chronic study in dogs, by capsule
- No effects on ovaries or uterus



## **Female Reproductive Toxicity of Chloroform (2): Data From Developmental Toxicity Studies**

### *Rats, inhalation*

- Reduced pregnancy rate or complete resorption of litters
- Decreased litter size and/or increased resorption frequency

### *Mice, inhalation*

- Reduced pregnancy rate and/or increased resorptions

### *Rats, oral*

- No effects on live litter size or resorption frequency

### *Rabbits, oral*

- Complete abortion of litters, not clearly related to dose



# **Summary of DART Effects Reported Following Chloroform Exposure**

## **Developmental**

- Decreased pregnancy rate
- Increased resorptions
- Decreased fetal weight and length

## **Male Reproductive**

- Abnormal sperm

## **Female Reproductive**

- Decreased pregnancy rate
- Increased resorptions and whole-litter abortions

